


EPA Reviewer: Lisa Austin, Ph.D.

Signature: 

Registration Action Branch 1, Health Effects Division (7509C)

Date: 9/20/09

Template version 02/06

TXR#: 0055057

**HED Executive Summary Cover for the attached OECD Formatted
DATA EVALUATION RECORD****STUDY TYPE:** 28-Day Oral Toxicity [feeding capsule]-[dog]; OPPTS 870.3150 [§82-1b]
(rodent); OECD 409.**PC CODE:** 118203**DP BARCODE:** D349929**TEST MATERIAL (PURITY):** BAS 800 H (93.8%)**SYNONYMS:** AC 433379; BASF Reg. No. 4054449, saflufenacil**CITATION:** Kaspers, U., Deckardt, K., Kaufmann, W. et al. (2005) BAS 800 H – Subacute oral toxicity study in Beagle dogs Administration via gelatin capsules for 4 weeks. Experimental Toxicology and Ecology, BASF AG, Ludwigshafen, FRG. Report Number(s) 40D0414/01164. November 14, 2005. MRID 47128112. Unpublished.**SPONSOR:** BASF Aktiengesellschaft, Ludwigshafen/Rhein, FRG.**EXECUTIVE SUMMARY:**

In a 4-week oral toxicity study (MRID 47128112), BAS 800 H (93.8%, Lot# COD - 000515) was administered daily via gelatin capsules to purebred Beagle dogs, 4/sex/group, at nominal doses of 0, 30, 100, or 300 mg/kg bw/d.

Treatment had no effects on mortality, body weight and body-weight gain, food consumption and food efficiency, or gross pathology.

Dark brown discolored feces were observed in all male and female dogs at 100 and 300 mg/kg bw/d groups. Treated-related hematological findings were decreased (10-24%) erythrocyte counts (10-17%), hemoglobin concentration (18-24%), and hematocrit (17-22%) values in both males and females at 300 mg/kg bw/d. Decreased values for mean corpuscular volume (5-8%), and mean corpuscular hemoglobin (9-10%), and mean corpuscular hemoglobin concentration (11-48%) were also recorded in males and females at 100 and 300 mg/kg bw/d. Although the magnitude of the decreases was small and there was no clear dose-response relationship, the effects were considered biologically significant because the blood was known to be the target for BAS 800 H. Alkaline phosphatase activity was higher in males (265%) and females (366%) at 300 mg/kg bw/d. Examination of porphyrin levels in the plasma, urine, and feces showed significant increases in all test groups. The increases at 30 mg/kg bw/d, in the absence of any other adverse effects, were not considered toxicologically important. At terminal sacrifice, absolute and relative weights of the liver (11-18%) and spleen (21-60%) of males and females at 300 mg/kg bw/d were significantly higher than those of control animals. Absolute and relative

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weights in kidney (increased 9-18%) and thymus (decreased 14-40%) were altered though not significantly in 300 mg/kg bw/d males and females. Histological examination revealed increased incidence of iron storage in the liver (2-3 vs 0/4 in controls), extramedullary hematopoiesis in the spleen (2-4 vs 0/4 in controls), and bone marrow hyperplasia (4 vs 0/4 in controls) in male and female dogs at 300 mg/kg bw/d.

The LOAEL in both male and female dogs was 100 mg/kg bw/d based upon decreased mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration, bone marrow hyperplasia, increased iron storage in the liver and extramedullary hematopoiesis in the spleen. The NOAEL was 30 mg/kg bw/d.

This 28-day oral toxicity study in dogs is acceptable, non-guideline range-finding study and does not satisfy the guideline requirement for a 90-day oral toxicity study (OPPTS 870.3100; OECD 408) in dogs.

COMPLIANCE: Signed and dated GLP, Quality Assurance, Flagging and Data Confidentiality statements were provided.

This Executive Summary was prepared for the United States Environmental Protection Agency, Office of Pesticide Program, Health Effects Division Use.

Much of the text was generated by the submitter(s) in OECD format. However, this document has undergone critical scientific analysis in comparison to the study report and modified as needed.



Reviewer #: Steve Wong, Ph.D., Date: April 24, 2008

APPLICANT: BASF Corporation

STUDY TYPE: Short-term oral (4-week) toxicity feeding study in dog; OECD 407.

TEST MATERIAL (PURITY): BAS 800 H (93.8%)

SYNONYMS: AC 433379; BASF Reg. No. 4054449

CITATION: Kaspers, U., Deckardt, K., Kaufmann, W. *et al.* (2005) BAS 800 H – Subacute oral toxicity study in Beagle dogs Administration via gelatin capsules for 4 weeks. Experimental Toxicology and Ecology, BASF AG, Ludwigshafen, FGR. Report Number(s) 40D0414/01164. BASF Doc ID 2007/7004136. November 14, 2005. Unpublished. [PMRA #1547034]

SPONSOR: BASF Aktiengesellschaft, Ludwigshafen/Rhein, FRG

EXECUTIVE SUMMARY:

In a 4-week oral toxicity study, BAS 800 H (93.8%) was administered daily via gelatine capsules to purebred Beagle dogs, 4/sex/group, at 0, 30, 100, or 300 mg/kg bw/d. Treatment had no effects on mortality, body weight and body-weight gain, food consumption and food efficiency, ophthalmoscopy, or gross pathology. Dark brown discoloured feces were observed in male and female dogs at 100 and 300 mg/kg bw/d groups. Treated-related hematological findings were decreased erythrocyte counts, hemoglobin concentration, and hematocrit values in both males and females at 300 mg/kg bw/d. Decreased values for mean corpuscular volume, and mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration were also recorded in males and females at 100 and 300 mg/kg bw/d. Although the magnitude of the decreases was small and there was no clear dose-response relationship, the effects were considered biologically significant because the blood was known to be the target for BAS 800 H. Alkaline phosphatase activity was higher in males and females at 300 mg/kg bw/d. Examination of porphyrin levels in the plasma, urine, and feces showed significant increases in all test groups. The increases at 30 mg/kg bw/d, in the absence of any other adverse effects, were not considered toxicologically important. At terminal sacrifice, absolute and relative weights of the liver and spleen of males and females at 300 mg/kg bw/d were significantly higher than those of control animals. Histological examination revealed increased iron storage in the liver, extramedullary hematopoiesis in the spleen, and hypertrophy of the bone marrow of male and female dogs at 300 mg/kg bw/d. The LOAEL in both male and female dogs was 100 mg/kg bw/d based upon microcytic hypochromic anemia resulting from altered porphyrin metabolism. The NOAEL was 30 mg/kg bw/d.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS:

| | |
|----------------------------|---|
| 1. Test material: | BAS 800 H |
| Description: | Solid / bright-beige; stored at room temperature |
| Lot/Batch #: | COD - 000515 |
| Purity: | 93.8% a.i. |
| Compound stability: | The stability under the storage conditions present in this study was guaranteed by the Certificate of Analysis. The homogeneity of BAS 800 H was confirmed by analysis. |
| CAS #: | 372137-35-4 |

2. **Vehicle and/or positive control:** BAS 800 H was administered via gelatine capsules.

3. Test animals:

| | | |
|--|--|--|
| Species: | Dog | |
| Strain: | Purebred Beagle | |
| Age/weight at study initiation: | Age: 8 to 9 months Mean weight: ♂ = 13.3 (11.9 – 14.4); 12.5 (9.5 – 14.6) kg | |
| Source: | BASF Beagle Colony | |
| Housing: | Floor area about 6 m ² (inner kennel about 1.5 m ² ; outer kennel about 4.5 m ²) | |
| Diet: | Dog maintenance KLIBA laboratory diet (pellets); Switzerland; ~400g/day | |
| Water: | Demineralized water, adjusted with drinking water to about 2° hardness; <i>ad libitum</i> | |
| Vaccination: | Distemper, hepatitis, leptospirosis, parvovirus, rabies and deworming at regular intervals | |
| Environmental conditions: | Temperature: Humidity: Air changes: Photoperiod: | Heating of the air supply was provided in the winter Ambient humidity Ventilation by forced ventilation system Natural day/night cycle with artificial light as required during working hours |
| Acclimation period: | At least seven days prior to application | |

B. STUDY DESIGN:

1. **In life dates:** Start: February 1, 2005 End: March 4, 2005

2. **Animal assignment:** Animals were assigned to test groups via a randomization protocol provided by a computer. The test groups are noted in Table 1.

Table 1: Study design

| | ♂ | | | | ♀ | | | |
|------------|---|----|-----|-----|---|----|-----|-----|
| mg/kg bw/d | 0 | 30 | 100 | 300 | 0 | 30 | 100 | 300 |
| N | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |

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3. Dose preparation and analysis:

The appropriate amounts of BAS 800 H, adjusted on the basis of individual animal's weekly body weight, was weighed and placed in gelatine capsules (stomach-soluble hard gelatine capsules). The prepared capsules were stored at room temperature.

4. Statistics:

| Parameter | Statistical test* | Reference |
|---|--|--|
| Food consumption, body weight, body weight change | A comparison of each group with the control group using the Dunnett-test (2-sided) for the hypothesis of equal means | Winer, B.J. (1971): Statistical principles in experimental design. McGraw-Hill New York, 2 nd edition. Dunnett, C.W. (1955): A multiple comparison procedure for comparing several treatments with a control. JASA, Vol. 50, 1096 - 1121 Dunnett, C.W. (1964). New tables for multiple comparisons with a control. Biometrics, Vol. 20, 482 - 491 |
| Clinical pathology parameters, except reticulocytes and differential blood count | Non-parametric one-way analysis using Kruskal-Wallis test (2-sided). If $p \leq 0.05$, a pair-wise comparison of each dose group with the control group was performed using Wilcoxon-test (2-sided) for the equal medians | Siegel S. (1956): Non-parametric statistics for behavioral sciences. McGraw-Hill New York |
| Urinalysis, except volume, color, turbidity and specific gravity | Pair-wise comparison of each dose group with the control group using Fisher's exact test for the hypothesis of equal proportions | Siegel S. (1956): Non-parametric statistics for behavioral sciences. McGraw-Hill New York |
| * Significantly different ($p < 0.05$) from the control; ** Significantly different ($p < 0.01$) from the control | | |

C. METHODS:

1. Observations:

The dogs were examined for signs of toxicity or mortality twice a day on weekdays and once a day on Saturdays, Sundays and public holidays.

Detailed clinical observations were conducted for all animals prior to the administration period and thereafter at weekly intervals. Parameters examined were as follows:

| | | | | | |
|------------------------------------|------------|-------------|--------------------|------------|----------------------------|
| activity / arousal level | skin | tremors | lacrimation | fur | mucosal membranes |
| abnormal behaviour during handling | posture | respiration | impairment of gait | pupil size | visible swellings / masses |
| feces (appearance / consistency) | salivation | convulsions | abnormal movements | urine | |

2. Body weight:

Body weight was determined on day -7, on the day before the administration period (day -1), and beginning on day 7, on weekly intervals.

3. Food consumption:

Food intake was determined each working day, starting on day -7 (beginning of the adaptation period) and calculated as mean food consumption in grams per dog per day. The dogs were offered food before the administration of the gelatine capsules for a period of up to two hours. Any food left over was weighed thereafter and subtracted from the amount of food offered. Food efficiency was calculated for each animal at weekly intervals on the basis of body weight changes and the total amount of food consumed during

this period, using the formula below:

$$\frac{BW_x - BW_{x-7}}{FC} \times 100$$

BW_x = Body weight on day x (in g)
 BW_{x-7} = Body weight on day x - 7 (in g)
 FC = Total daily food consumption (in g) from day x-7 to day x-1

4. **Ophthalmoscopic examination:** Ophthalmoscopic examination was not conducted.

5. **Hematology & clinical chemistry:**

Blood was taken from non-anesthetised, fasted animals from the vena cephalica antebrachii. Blood sampling occurred prior to dosing (on study day -14 or 13) and on study day 27. The checked (x) parameters were examined.

a. **Hematology:**

| | | | | | |
|---------------------------|---|---|---|---|--------------------|
| x | Hematocrit (Hct)* | x | Leukocyte differential count* | x | Reticulocyte count |
| x | Hemoglobin (Hb)* | x | Mean corpuscular Hb (MCH) | x | Platelet count |
| x | Leukocyte count (WBC)* | x | Mean corpuscular Hb concentration(MCHC) | | |
| x | Erythrocyte count (RBC)* | x | Mean corpuscular volume (MCV) | | |
| x | Blood clotting measurements*, prothrombin time (Thromboplastin time; Clotting time) | | | | |
| * Recommended by OECD 407 | | | | | |

b. **Clinical chemistry:**

| Electrolytes | | | Others | | |
|---------------------------|---|---|-------------|---------------|-------------------------------|
| x | calcium* | x | sodium* | x | total protein (TP)* |
| x | chloride* | x | potassium* | x | total cholesterol |
| x | magnesium | x | phosphorus* | x | albumin* |
| Enzymes | | | x | globulins | x |
| x | alkaline phosphatase (AP) | | x | glucose* | x |
| x | serum alanine amino-transferase (ALT/SGPT)* | | | triglycerides | x |
| x | serum aspartate amino-transferase (AST/SGOT)* | | | | total bilirubin* |
| x | creatine phosphokinase | | | | serum protein electrophoresis |
| x | gamma glutamyl transferase (GGT)* | | | | x |
| | cholinesterase (ChE) | | | | total porphyrins in plasma |
| | lactic acid dehydrogenase (LDH) | | | | x |
| | glutamate dehydrogenase | | | | total porphyrins in urine |
| | ornithine decarboxylase* | | | | x |
| * Recommended by OECD 407 | | | | | |

6. **Urinalysis:**

Urinalysis was conducted prior to the dosing period (study day -12 or -11) and at the end of the study (study day 23 or 24). For urinalysis the individual animals were transferred to metabolism cages (food withdrawn, about 500 mL of water), and urine was collected overnight. The following parameters (X) were analyzed:

| | | | | | | | | | | | |
|---|--------|---|------------------|---|---------|---|--------------|---|-----------|---|----------|
| x | volume | x | specific gravity | x | glucose | x | urobilinogen | x | ketones | x | sediment |
| x | pH | x | color, turbidity | x | protein | x | blood | x | bilirubin | | |

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7. Sacrifice and pathology:

All animals that died and those sacrificed on schedule were subjected to gross pathological examination and the checked (x) tissues were collected for histological examination. The (xx) organs were weighed.

| Digestive system | | | | Cardiovascular/hematological | | | | Neurological | |
|------------------|-----------------|----|--------------|------------------------------|---------------------------|----|-------------|--------------|------------------------|
| | tongue | x | cecum | x | aorta | x | bone marrow | xx | brain |
| x | salivary glands | x | colon | xx | heart* | x | lymph nodes | xx | pituitary |
| x | esophagus | x | rectum | xx | spleen* | xx | thymus | x | sciatic nerve |
| x | stomach | xx | liver** | Urogenital | | | | x | spinal cord (3 levels) |
| x | duodenum | x | gall bladder | xx | kidneys** | | | x | eyes (optic nerve) |
| x | jejunum | x | pancreas | x | urinary bladder | | | Glandular | |
| x | ileum | | | xx | testes * | | | xx | adrenal gland** |
| Respiratory | | | | xx | epididymides | | | x | mammary gland |
| x | trachea | x | nose | xx | prostate | | | x | parathyroids |
| x | lung | x | pharynx | x | seminal vesicle | | | x | thyroids |
| x | nasal cavity | x | larynx | xx | ovaries | | | | lacrimal gland |
| | | | | xx | uterus and vagina | | | | |
| Others | | | | | | | | | |
| x | bone | x | skin | x | gross lesions and masses* | | | x | target organs* |

* Recommended by OECD 407; ** Organ weight required by OECD 407

II. RESULTS

A. Observations:

1. Clinical signs of toxicity:

Dark brown discoloured feces were observed in all dogs at 100 and 300 mg/kg bw/d throughout the entire study period. There were no treatment-related clinical signs at 30 mg/kg bw/d.

2. Mortality: All animals survived the study period.

B. Body weight and weight gain:

There was no statistically significant deviation in the body weight or the body weight gain in any of the test groups (both male and female).

C. Food consumption and food efficiency:

All male dogs consumed the daily ration of food (400 g/dog). All females consumed the daily ration of food except on 4 occasions. A female dog at 100 mg/kg bw/d did not consume the daily ration on days 21, 24, and 28. One female at 300 mg/kg bw/d did not consume the daily ration on day 24. These isolated findings were not considered to be treatment related. There were no treatment-related effects on the food efficiency in any test group (males and females).

D. Blood analyses:

1. Hematology:

Treated-related hematological findings were decreased erythrocyte counts, hemoglobin concentration (Hb), and hematocrit (Hct) values in both males and females at 300 mg/kg bw/d. Decreased values for mean corpuscular volume (MCV), and mean corpuscular hemoglobin (MCH), and mean corpuscular

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 BASF [BAS] DACO 4.3.2 / OECD IIA 5.3.3

hemoglobin concentration (MCHC) were also recorded in males and females at 100 and 300 mg/kg bw/d. Although the magnitude of the decreases was small and there was no clear dose-response relationship, the effects were considered biologically significant because the blood was known to be the target for BAS 800 H. The white blood cell counts in males and females at 300 mg/kg bw/d were clearly increased, although the increase did not attain statistical significance. In the differential blood count the increases in leukocytes were associated with increases in polymorphonuclear neutrophils.

It was stated in the study report that polychromasia, anisocytosis and microcytosis were seen in the blood of males and females at 300 mg/kg bw/d. Polychromasia was also detected in dogs of both sexes at 100 mg/kg bw/d. In addition, platelets were increased in males at 100 and 300 mg/kg bw/d and in females at 300 mg/kg bw/d.

Table 2. Selected hematological values, mean±SD

| mg/kg bw/d | ♂ (N = 4/group) | | | | ♀ (N = 4/group) | | | |
|---------------------------------|-----------------|-----------|------------|------------|-----------------|-----------|------------|------------|
| | 0 | 30 | 100 | 300 | 0 | 30 | 100 | 300 |
| RBC, 10 ¹² /L | 6.94±0.12 | 6.68±0.45 | 7.32±0.47 | 5.75±1.00 | 7.00±0.34 | 7.08±0.35 | 7.97±0.34* | 6.33±0.71 |
| Hb, mmol/L | 9.7±0.2 | 9.3±0.7 | 9.3±0.7 | 7.4±1.1 | 10.3±0.6 | 9.9±0.5 | 10.3±0.6 | 8.4±1.0* |
| Hct, % | 46.6±0.6 | 45.1±3.6 | 45.8±3.3 | 36.5±5.2 | 49.3±3.4 | 47.8±2.3 | 50.0±2.4 | 41.1±4.4* |
| MCV, fL | 67.2±1.1 | 67.5±2.1 | 62.6±0.5* | 63.6±1.7* | 70.3±1.8 | 67.5±2.3 | 62.7±1.3* | 65.0±0.8* |
| MCH, fmol | 1.40±0.03 | 1.40±0.04 | 1.27±0.02* | 1.29±0.03* | 1.47±0.03 | 1.40±0.05 | 1.30±0.04* | 1.33±0.02* |
| MCHC, mmol/L | 22.8±0.20 | 20.7±0.18 | 20.3±0.19* | 20.3±0.38 | 20.9±0.24 | 20.8±0.17 | 20.7±0.37 | 20.5±0.24 |
| WBC, 10 ⁹ /L | 11.8±2.38 | 12.2±1.27 | 12.9±2.71 | 15.2±3.83 | 11.6±2.05 | 12.1±2.58 | 12.5±2.00 | 17.2±3.50 |
| Neutrophils, 10 ⁹ /L | 7.02±1.58 | 7.21±0.61 | 8.34±2.40 | 9.33±2.92 | 6.80±1.73 | 7.21±1.85 | 7.38±0.96 | 10.39±2.3 |
| Lymphocyte, 10 ⁹ /L | 3.91±0.65 | 4.05±0.65 | 3.69±0.27 | 4.63±0.90 | 3.93±0.40 | 4.06±0.59 | 4.32±0.97 | 5.67±0.92 |
| Platelets, 10 ⁹ /L | 333±38 | 332±41 | 424±17* | 560±102* | 372±44 | 332±61 | 368±12 | 552±97* |
| PTT, seconds | 11.9±0.4 | 11.6±0.6 | 10.9±0.4* | 10.3±0.3* | 11.3±0.7 | 12.0±0.5 | 10.5±0.7 | 10.4±0.4 |

Data taken from Table IB, pages 72-87, 138, and 142 of Report; PTT = Partial thromboplastin time;

* ≤0.05; ** ≤0.01; bold values are considered treatment-related

2. Clinical chemistry:

Serum enzyme examinations revealed statistically significant increased alkaline phosphatase activities in males and females at 300 mg/kg bw/d. No other enzyme activities were adversely affected although some values were statistically significantly different from the control values. Blood chemistry analyses showed no significant treatment-related findings.

Table 3. Alkaline phosphatase (AP) values, mean±SD

| mg/kg bw/d | ♂ (N = 4/group) | | | | ♀ (N = 4/group) | | | |
|------------|-----------------|------------|-----------|------------|-----------------|-----------|------------|------------|
| | 0 | 30 | 100 | 300 | 0 | 30 | 100 | 300 |
| AP, µkat/L | 1.48±0.30 | 2.39±0.31* | 2.47±0.65 | 5.40±0.79* | 1.35±0.23 | 1.78±0.46 | 2.88±1.08* | 6.29±1.50* |

Data taken from Table IB, pages 88-99 of Report; * ≤0.05; ** ≤0.01; bold values are considered treatment-related

3. Porphyrin analysis: Table 4

Table 4. Porphyrin values, mean±SD

| mg/kg bw/d | ♂ (N = 4/group) | | | | ♀ (N = 4/group) | | | |
|-----------------------------|-----------------|------------------|-----------------|------------------|-----------------|-----------------|------------------|-------------------|
| | 0 | 30 | 100 | 300 | 0 | 30 | 100 | 300 |
| Plasma porphyrin nmol/L | 3.9 ±0.6 | 16.5 ±3.4* | 49.2 ±22.9* | 121.5 ±59.7* | 4.8 ±1.0 | 16.5 ±5.1* | 43.8 ±26.0* | 109.8 ±52.3* |
| Urine porphyrin, µg/L | 13.1 ±4.8 | 35.4 ±21.4 | 152.8 ±14.4* | 383.8 ±215.1* | 3.1 ±3.9 | 16.5 ±11.6 | 197.1 ±107.6* | 463.8 ±311.7* |
| Fecal porphyrin, µmol/kg df | 35.9 ±28.1 | 333.3 ±151.4* | 1147.7 ±730* | 951.7 ±635.9* | 51.5 ±29.4 | 302.0 ±90.9* | 1247.4 ±926.7 | 1563.6 ±312.6* |

Data taken from Table IB, pages 100-101 of Report; * ≤0.05; ** ≤0.01; bold values are considered treatment-related

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Marked, dose-dependent increases in total porphyrin were found in urine, plasma, and feces of all treatment groups of either sex.

E. Urinalysis:

Except for the increases in porphyrin levels in male and female dogs at 100 and 300 mg/kg bw/d, there were no other treatment-related findings.

F. Sacrifice and pathology:

1. Organ weight:

There was an increase in absolute and relative weights of the liver and spleen of males and females at 300 mg/kg bw/d, which was regarded to be treatment-related. Other findings were considered normal biological variations or due to secondary effects to treatment with minimal biological significance. The assessment of treatment-related adverse effects on organ weights was difficult due to the low number of dogs used per group.

Table 5. Selected organ weight values, mean±SD

| | | ♂ (N = 4/group) | | | | ♀ (N = 4/group) | | | |
|------------|-----|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| mg/kg bw/d | | 0 | 30 | 100 | 300 | 0 | 30 | 100 | 300 |
| BW, g | | 13850 ±666 | 13300 ±668 | 13675 ±685 | 13475 ±842 | 12575 ±685 | 12800 ±913 | 12575 ±613 | 12200 ±1992 |
| Liver | g | 398±30 | 393±45 | 426±29 | 440±11 | 345±30 | 364±30 | 367±6 | 408±54 |
| | %BW | 2.89±0.34 | 2.95±0.25 | 3.13±0.37 | 3.28±0.24 | 2.74±0.13 | 2.86±0.30 | 2.92±0.10 | 3.36±0.17 |
| kidneys | g | 62.1±4.1 | 64.8±3.5 | 68.2±7.9 | 67.9±6.1 | 55.7±2.4 | 57.9±4.5 | 58.4±3.1 | 63.4±8.7 |
| | %BW | 0.449 ±0.030 | 0.488 ±0.027 | 0.498 ±0.038 | 0.503 ±0.015 | 0.444 ±0.027 | 0.456 ±0.067 | 0.465 ±0.031 | 0.522 ±0.040 |
| Spleen | g | 32.6±5.4 | 28.7±1.6 | 31.1±2.5 | 39.6±9.0 | 29.8±4.0 | 29.5±5.1 | 35.4±5.2 | 47.5±22.9 |
| | %BW | 0.236 ±0.042 | 0.217 ±0.021 | 0.228 ±0.025 | 0.297 ±0.083 | 0.236 ±0.022 | 0.232 ±0.046 | 0.283 ±0.054 | 0.374 ±0.136 |
| Thymus | g | 8.21±3.00 | 7.99±1.77 | 6.96±2.84 | 6.87±2.07 | 7.10±1.51 | 7.36±2.77 | 7.40±2.21 | 4.23±2.64 |
| | %BW | 0.059 ±0.022 | 0.06 ±0.012 | 0.05 ±0.018 | 0.051 ±0.016 | 0.057 ±0.013 | 0.057 ±0.02 | 0.059 ±0.017 | 0.034 ±0.017 |

Data taken from Table IC, pages 102-107 of Report; * ≤0.05; ** ≤0.01; bold values are considered treatment-related

2. Gross pathology: There were no treatment-related findings.

3. Microscopic pathology:

Substance-induced findings were observed in the liver (iron storage), the spleen (extramedullary hematopoiesis) and the bone marrow (hypertrophy) of male and female dogs at 300 mg/kg bw/d, and single dogs at 100 mg/kg bw/d.

Table 6. Selected microscopic findings, number of dogs affected

| | | ♂ (N = 4/group) | | | | ♀ (N = 4/group) | | | |
|-------------|------------------------------|-----------------|----|-----|-----|-----------------|----|-----|-----|
| mg/kg bw/d | | 0 | 30 | 100 | 300 | 0 | 30 | 100 | 300 |
| Bone marrow | Hyperplasia | 0 | 0 | 0 | 4 | 0 | 0 | 1 | 4 |
| liver | Iron storage | | | 1 | 2 | | | | 3 |
| Spleen | Extramedullary hematopoiesis | | | 1 | 2 | | | | 4 |

Data taken from Table IC, pages 107-109 of Report; bold values are considered treatment-related

III. DISCUSSION

A. Authors' conclusions:

The LOAEL in both males and females was 100 mg/kg bw/d based on microcytic hypochromic anemia resulting from altered porphyrin metabolism. As a postulated compensatory response, increases in extramedullary hematopoiesis in the spleen and liver were also noted in some treated dogs. Porphyrin changes observed at 30 mg/kg bw/d, in the absence of any other adverse effects, are not considered toxicologically important. The NOAEL was 30 mg/kg bw/d.

B. Reviewer's comments:

The study was properly conducted and reported. The authors' conclusions are acceptable.

C. Deficiencies:

Table IB, page 81 of Report: The table on this page should have presented the day 27 mean differential blood counts of males; the female data are presented instead. As individual animal data on differential white blood cell counts are available on pages 138 and 142, submission of the missing table is not necessary.